Multiple Myeloma

A Review of 26 Cases

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• **Multiple myeloma is a rare, malignant disease of bone marrow which affects principally the vertebrae, ribs, pelvis and skull but may involve any part of the skeleton. Severe demineralization and destructive lesions of bones, producing severe pain and debility, are distinctive features. The disease is further distinguished by abnormalities of blood proteins and in some cases by the excretion in the urine of Bence-Jones protein, which seldom, if ever, is found in association with any other disease.**

X-ray examination is frequently helpful. In 22 of 24 cases (of a series of 26 cases) in which films were available, definite abnormalities were noted. Spontaneous fractures, particularly of vertebrae, are common.

The diagnosis of the disease rests on the identification of the myeloma cell. This is best accomplished by aspiration of bone marrow. In several of the 26 cases in the series diagnosis was made by a neurosurgeon at the time of operation to relieve pressure on the spinal cord. The myeloma cell has a very characteristic appearance.

In the present series the average duration of life after the onset of symptoms was only nine months. One patient, however, survived for at least ten years.

On the 30th of October, 1845, Mr. M., "a highly respectable tradesman," placed himself in the care of Dr. William MacIntyre, who subsequently reported the case in the *Transactions of the Medico-Chirurgical Society* in 1850.[22] When first seen, the patient was confined to home by "excruciating pains of the chest, back and loins, from which he had been suffering more or less for upwards of twelve months." He was treated with bloodletting "to the amount of a pound" by the application of leeches, cups and blisters, and by the administration of such tonics as steel and quinine and tincture of aconite. Despite these and a host of other medications, pain, weakness and emaciation progressed, and on the first day of January, 1848, he "died exhausted in the full possession of his mental faculties and evincing, in the supreme hour of suffering, the same admirable fortitude and patient endurance which he had displayed throughout the whole course of his illness."

In all likelihood, this case would have passed into obscurity—indeed, probably never would have been reported—were it not for a urinalysis.

It was the custom one hundred years ago for physicians to do laboratory tests themselves. Dr. MacIntyre thus recorded, in part, his observations of the urine:

". . . Treated with heat to ebullition but not under that, it was found to abound in *animal matter*, which, when isolated in this way, exhibited all the characters of albumin. With nitric acid, however, this urine displayed abnormalities of a remarkable kind. On the addition of the acid, no immediate precipitation took place; on the contrary, the urine previously cloudy or turbid, became instantly clear and retained its transparency for an hour or an hour and a half, when it was found to be formed into a firm yellow mass . . . which underwent complete solution on the application of heat, but again consolidated on cooling."

MacIntyre was intrigued by these findings and he conducted experiments in an attempt to determine the precise nature of the substance resulting from the action of nitric acid which he referred to as "animal matter." Furthermore, a specimen of the urine was sent to a distinguished physician and chemist of the day, Sir Henry Bence-Jones,[7] who reported his findings to the Royal Society in April, 1847. History seems clearly to indicate that MacIntyre first discovered this peculiar "animal matter," but it was Bence-Jones who first published a description of it. For this reason it has ever since been known as Bence-Jones protein.

Dalrymple[9] performed a microscopic examination of sections of a rib and two lumbar vertebrae of MacIntyre's patient; and he not only described but made a sketch of what he saw. He noted "certain nucleolated nucleated cells" in sections of the ribs —but one would be hard pressed from Dalrymple's original drawing to identify these as myeloma cells.

Rustisky[25] (1873) generally is credited with being the first to describe this disorder under the name "multiple myelom." Otto Kahler[17] in 1889 differentiated it from osteomalacia, and noted the occurrence of bone pain and fragility, palpable bony enlargements or "tumors," the appearance of a distinc-

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tive kind of proteinuria first described by Bence-Jones, and the predilection to involve bones of the trunk. In 1928 Geschickter and Copeland[11] carefully reviewed every published case of myeloma in the world's literature up to that time—a total of 412—and added reports of 13 cases observed at the Johns Hopkins Hospital. In recent years several excellent reviews on this subject have been published.[1,2,4,19] A most extensive treatise on multiple myeloma is an admirable monograph by Snapper and his colleagues[27] (1953), based on 97 personally observed cases.

METHODS AND MATERIALS

Twenty-six cases of multiple myeloma observed at the California Hospital, Los Angeles, in the period 1942-56, inclusive, are the basis of this review. Of the 26 cases, 12 were diagnosed between 1942 and 1952, eight between 1952 and 1955, and six in 1956. It is likely that the increased incidence in recent years reflects greater awareness and improved diagnostic methods rather than an actual increase in the frequency of the disease.

Sex and Age of Patients. Thirteen of the patients were males, 13 females. (Although not of great moment, it should be noted that in most other studies 65 to 85 per cent of the patients were males.) The average age of all patients was 60 years; the average age of males was 58 years, of females 62 years. Twenty-one of the 26 patients were 50 years of age or older. Four patients were in the fifth decade of life, five in the sixth, twelve in the seventh and three in the eighth decade. One patient was 33 and one was 80 years of age.

Methods of Diagnosis. Diagnosis was established by bone marrow aspiration in nine cases, and by surgical biopsy in nine, by necropsy study in seven cases and on the basis of characteristic roentgenographic and biochemical data in one case. Upon careful review of the seven cases in which necropsy was done, the conclusion was reached that in five there was sufficient data either to suggest or establish a correct diagnosis ante mortem.

CLINICAL FEATURES

The incidence of various clinical features is shown in Table 1. Pain, by far the most common and outstanding symptom, occurred in 24 of 26 cases. In 16 cases it began slowly and increased to severity usually described as "terrific," "excruciating" or "agonizing." In several patients, onset of pain was abrupt, usually coinciding with the occurrence of a pathologic fracture. It was usually aggravated by coughing, sneezing, straining or any motion of the torso or extremities. Patients frequently discovered

TABLE 1.—*Incidence of Various Clinical Features in 26 Cases of Multiple Myeloma*

	Number	Per Cent
Pain	24	92
Pulmonary symptoms and signs	16	61
Superficial tenderness	14	54
Fever	13	50
Hemorrhagic manifestations	11	42
Gastrointestinal symptoms	10	38
Loss of weight	10	38
Palpable tumor	8	30
Neurological signs	6	23
Palpable liver	4	15
Palpable spleen	2	7

that if they could remain motionless they would have much less discomfort. Several came to dread the approach of a nurse or physician to the bedside, for fear that they would be moved or disturbed in any way and their pain thereby increased. As Snapper[27] graphically described the course of the illness, "The patient may become, in the last stages of the disease, a pain-wracked invalid, completely bedridden, forced to lie for unending hours in an unchanging position, requiring opiates around the clock."

Pain in multiple myeloma is generally believed due to osteolytic lesions occurring in bones subject to stress or motion. That the lesions *per se* are not painful is suggested by the fact that patients with multiple punched-out areas in the skull do not complain of pain. Only two of the patients in the present series had the cyclic pattern of exacerbations and remissions of pain described by Geschickter and Copeland.[11] Rather, the pain seemed to increase with the duration of the disease. In common with Bayrd and Heck,[4] of Snapper,[27] and Carson and colleagues,[8] we found pain in the back to be most common; it occurred in 20 of the 24 cases in which pain was a symptom. It was located in the lumbar region in 11 cases, in the thoracic area in six cases, in both thoracic and lumbar areas in two cases, and in the cervical area in one.

Sixteen patients had symptoms or signs of pulmonary disease. In order of frequency, these were pleurisy or pain of pleuritic type, bronchitis and bronchopneumonia. Such symptoms are not surprising inasmuch as patients with multiple myeloma are frequently debilitated and are confined to bed because of pain and paralysis.

Pronounced superficial tenderness was noted most frequently over the lumbar spine or ribs, but in several cases was over hip or shoulder joints. Usually it occurred over the sites of osteolytic lesions or pathologic fractures.

Thirteen of 26 patients (50 per cent) had fever during their hospital stay. Fever, which occurred in 13 patients during the time they were in hospital was always low-grade and never a striking or dis-

tinctive feature. In about two-thirds of the cases it was intermittent, and in one-third, remittent in type.

As to hemorrhagic manifestations, Snapper[27] and Adams and associates[1] reported abnormal bleeding in 35 per cent and 39 per cent of their cases, respectively. In the present series, epistaxis was the most common, occurring in about half the cases, followed by purpura and hemoptysis. Studies on blood coagulation were so few that even conjecture respecting the nature of the clotting defect is not permissible. However, according to Wintrobe,[29] the defect has never been satisfactorily explained. Several observers have expressed belief it may be related to hyperglobulinemia, which is a common feature of the disease.[19,27]

Symptoms referable to the gastrointestinal tract, such as constipation, anorexia, nausea and vomiting, were in no way unlike those which might be encountered in any debilitating process and were of no assistance in diagnosis. In four of the ten cases in which loss of weight occurred, the loss was considered "marked."

Palpable tumors due to large focal collections of myeloma cells (plasmacytomas) were located in the ribs in three cases, in cervical and axillary nodes in two cases and in the skull, thoracic spine and ilium in one case each.

Of the six patients with definite neurological abnormalities, one had paraplegia and paralysis of the right side of the face and tongue. (At autopsy in this case it was noted that the orbital plate of the left sphenoid bone was infiltrated and largely replaced by tumor tissue.) One patient had paralysis of the right arm and leg and of the left arm and one had weakness of both legs. Three had complete paraplegia, and in all three this was due to a compression of the cord by a myelomatous involvement of vertebrae. Diagnosis was established in these three cases by examination of tissue removed at the time of laminectomy done to decompress the spinal cord. Among the noninflammatory lesions of the spine producing cord compression, only metastatic carcinoma is more common than myeloma.[16,26]

LABORATORY DATA

Laboratory data on the present series are given in Table 2. A rapid erythrocyte sedimentation rate is characteristic of multiple myeloma; indeed, it is probably the most common abnormality noted in laboratory tests. It was present in 97 per cent of the patients in the series reported by Bayrd and Heck[4] and in 89 per cent of the series Snapper[27] reported. The test was performed on only seven patients in the present series; six had an accelerated rate. The fastest sedimentation rate was 76 mm. in one hour (Westergren); the average was 54 mm. in one hour. Rates as high as 176 mm. in an hour have been reported.[4] Acceleration of the sedimentation rate is due to the presence of increased plasma globulin or fibrinogen or both. In this study serum globulin determinations were made in four cases in which the sedimentation rate was accelerated; in all four, serum globulin was increased.

TABLE 2.—*Analysis of Laboratory Data—Multiple Myeloma*

No. Cases with Data Available		No. of Patients	Per Cent
7	Increased sedimentation rate	6	86
12	Hyperglobulinemia	8	67
22	Anemia	11	50
10	Uremia (nonprotein nitrogen above 40 mg. per cent)	5	50
26	Rouleaux formation	10	38
6	Thrombocytopenia (below 100,000 cu. mm.)	2	33
9	Serum calcium abnormalities	3	33
6	Serum phosphate abnormalities	2	33
26	Leukopenia (WBC below 5,000 cu. mm.)	8	31
25	Plasma cells in peripheral blood	5	20
16	Bence-Jones proteinuria	3	19

Hyperglobulinemia was present in eight of twelve cases in this study. This corresponds closely to that reported by Adams and co-workers[1] (67 per cent), by Bayrd and Heck[4] (73 per cent) and by Carson and co-workers[8] (72 per cent). When present, it is an important diagnostic finding. Although hyperglobulinemia may occur in a variety of diseases, its coexistence with osteolytic lesions substantially narrows the field of diagnostic possibilities. Furthermore, globulin fractions in multiple myeloma as determined by fractionation and electrophoretic studies present certain features not seen in other disease states associated with hyperglobulinemia.[1,27] We would like to emphasize what other observers have pointed out, that hyperglobulinemia causes a variety of alterations in hematologic tests. Not only does it produce an increase in sedimentation rate but is also responsible for excess rouleaux formation which makes it difficult and at times impossible to obtain a count of erythrocytes. Furthermore, it imparts a rather distinct bluish color to blood smears stained with Wright's solution. It may also cause autohemagglutination, making cross-matching of blood at times extremely difficult. Abnormalities of serum proteins in multiple myeloma have been extensively studied by both chemical and electrophoretic methods. A discussion of this is beyond the scope of this review. The studies of Adams and colleagues[1] and of Waldenström[28] are recommended.

Anemia is common in multiple myeloma. Eleven of the 22 patients on whom hemoglobin data was available had hemoglobin content of less than 11.0 gm. per 100 cc. of blood. Twelve had erythrocyte content of less than 4,000,000 per cubic mm., and

five had less than 3,000,000 per cubic mm. There is nothing in the cell count which specifically suggests myeloma, but any unexplained anemia should dictate bone marrow study.

Uremia (nonprotein nitrogen content above 40 mg. per 100 cc. of serum) was present in five of ten patients on whom this data was available. Fifteen of the 26 patients in the entire series had some evidence of renal dysfunction as manifest by azotemia, albuminuria (2-plus or more), cylindruria and/or hematuria. Bell[5,6] expressed the opinion that renal impairment in this disease is due to tubular obstruction caused by deposition of Bence-Jones protein. However, renal function studies on patients with multiple myeloma suggested that impairment of glomerular filtration may also be an important factor.[27] Because of renal abnormalities, patients with multiple myeloma are often first believed to have nephritis. A point which aids in distinguishing multiple myeloma from Bright's disease is that the renal dysfunction associated with multiple myeloma does not produce hypertension. In the series Bell[5] reported, only 26 per cent of patients were hypertensive and in the present study only 20 per cent—an incidence probably no higher than the incidence of hypertension among a random sampling of population of the same age.

Excessive rouleaux formation is another distinctive feature of this disease. Adams and co-workers[1] noted this phenomenon in 59 per cent, and Bayrd and Heck[4] in 60 per cent of the cases in their series. It occurred in 38 per cent (10 of 26 cases) in the present study. In some cases, laboratory technicians, noting excessive rouleaux formation on the initial blood smear at the time of admittance of the patient to hospital, were first to suggest the proper diagnosis. Rouleaux formation was first described in 1777,[15] but it was not until 1932 that Reimann[24] pointed out its occurrence in multiple myeloma.

Leukopenia (leukocytes below 5,000,000 per cu. mm.) occurred in eight of the 26 cases (31 per cent) in this series. Snapper[27] noted it in 40 per cent of patients, and Bayrd and Heck[4] in 33 per cent. The differential of cells, in general, was not unusual or distinctive. However, in a few cases a shift to the left was noted. Thrombocytopenia is rather uncommon in this disease. In this study it was noted in only two patients, both in terminal stage of disease.

Rapid skeletal demineralization may occur in this disease, with consequent hypercalcemia. However, the reports in the literature vary considerably as to the incidence of this condition, ranging from 20 per cent to 55 per cent.[1,4,8,13] In our studies, serum calcium determinations were made in nine patients. The values were normal in six cases, increased in two and decreased in one. Serum phosphate determinations were made in six patients; the values were normal in four, and elevated in two. No values below normal were obtained, a point of some assistance in the differential diagnosis from hyperparathyroidism.

Plasma cells were observed in smears of peripheral blood in five of 25 cases (20 per cent). The average proportion of plasma cells was 10 per cent of the nucleated cells; in one patient, 56 per cent were plasma cells. Snapper[27] and Bayrd and Heck[4] reported, respectively, a 22 per cent and a 10 per cent incidence of this phenomenon.

Bence-Jones proteinuria was noted in only three of sixteen cases, or 19 per cent of the series. This incidence was lower than any reported in the available literature. It was reported in 45 per cent of the cases studied by Carson and colleagues,[8] in 49 per cent of Snapper's cases,[27] and in 56 per cent of the Mayo Clinic series.[4] We have no ready explanation for this pronounced disparity in this regard between our series and others, except to point out that in most cases only one test was done. Perhaps if it had been performed more often the observed incidence would have been higher. The object lesson to be drawn from this is that while the presence of Bence-Jones proteinuria is almost pathognomonic of the disease, failure to find it means little.

ROENTGEN ABNORMALITIES

X-ray studies of some portion of the skeleton were obtained in 24 cases; in 14 cases films were available for review. Although there is no roentgen picture which will permit unquestioned diagnosis of multiple myeloma, x-ray studies may nevertheless be quite helpful.[10,14]

In several cases in this series, information so obtained was the first clue toward a correct diagnosis. In 22 of 24 cases there were some abnormalities which to varying degrees were suggestive of multiple myeloma.

Generalized osteoporosis is probably the most common roentgenographic change. It has been repeatedly emphasized that this may be the only abnormality observed in x-ray films.[4,10] In our experience, however, it never occurred alone but was always accompanied either by focal areas of destruction or by pathologic fractures. Osteoporosis alone may not be of much diagnostic help, for many patients with multiple myeloma are of an age at which this is a normal finding. However, if it is extreme and widespread and is not confined merely to the vertebral column and the pelvis, the possibility of multiple myeloma should be considered.[27] Multiple focal areas of rarefaction of the skeleton without accompanying osteoblastic reaction are strongly suggestive of multiple myeloma, although metastatic carcinoma, reticulum cell sarcoma and hyperpara-

thyroidism may produce a very similar picture. The term "punched-out" has long been associated with this x-ray appearance but probably should be discarded.[14] Not infrequently the surrounding bone is so severely decalcified that there is little contrast between it and the osseous defect. Rather than having a "punched-out" appearance the lesions resemble moth-eaten areas in a porous fabric or impart to the bone an irregular honey-combed appearance. In this series osteolytic lesions were found in the skull and pelvis with about equal frequency. Next most commonly affected were vertebrae and ribs (Table 3). Sixteen patients upon whom x-ray studies were done had a total of 23 pathologic fractures. Snapper[27] found one or more fractures in 62 per cent of the cases he reported upon. Lumbar vertebrae, thoracic vertebrae and ribs were most commonly involved and were affected with about equal frequency. Next in order were cervical vertebrae and extremities.

TABLE 3.—*Roentgenologic Abnormalities in Bones in Multiple Myeloma*

TYPES
Osteoporosis
Pathologic Fractures
"Punched-Out" Lesions

DISTRIBUTION OF ABNORMALITIES	
"Punched-Out" Lesions	Pathologic Fractures
Skull	Thoracic vertebrae
Pelvis	Lumbar vertebrae
Lumbar vertebrae	Ribs
Thoracic vertebrae	Cervical vertebrae
Ribs	Extremities
Cervical vertebrae	

PATHOLOGICAL FINDINGS

The gross pathological changes in multiple myeloma, particularly with regard to the bones, may be so varied that a single composite description is impossible. Lichtenstein[20] described the various conditions in detail. It is interesting to note, however, that in the original report of this disease MacIntyre[22] gave a very lucid description of the necropsy observations in the case of Mr. M., which has proved to be a common pathological picture. He wrote in part:

". . . All the ribs throughout their length were soft and brittle, so that they could easily be cut by the knife and readily broken at any point by the exertion of a very moderate force. They have evidently lost much in size and weight as well as in consistency and tenacity; their outer casement or laminated portion was very thin, loose and fragile, yielding or cracking when pressed between the fingers and thumb; their interior was charged with a soft, gelatiniform substance of a blood-red color and an unctious feel. . . . The upper three divisions of the columna (spine) . . . all presented the same characters of softness and brittleness, but the dorsal and lumbar had evidently suffered most . . . their bodies scarcely equalling those of the cervical in thickness . . ."

The "soft gelatiniform substance" which, as MacIntyre observed, filled the marrow cavity was myeloma. Microscopically it is composed of aggregates or sheets of mononuclear cells with little intercellular supporting material. These cells usually are decidedly uniform in size, shape and staining properties, although some pleomorphism is occasionally seen. Definitive diagnosis of multiple myeloma depends upon identification of this cell. It is usually round or oval and from 9 to 11 microns in diameter, although immature cells may be as much as 20 to 40 microns in diameter.[20,27,29] A distinctive characteristic is an eccentrically placed nucleus containing one to three nucleoli. The nucleus is usually hyperchromatic; nuclear chromatin is frequently arranged in irregular coarse clumps. There may be a clear zone or halo surrounding the nucleus. The cytoplasm is usually light blue when stained with Wright's stain, or is eosinophilic with hematoxylin and eosin. It may contain vacuoles or azurophilic inclusions.

There has been some conjecture relative to the origin of the myeloma cell. Bayrd and Heck[4] expressed belief that it is derived from the reticulum cell. Myeloma may involve any bone but it has a predilection for bones with abundant red marrow, such as the sternum, ribs, vertebra, skull and long bones. Extraskeletal involvement with myeloma is not common and usually occurs concomitantly with osseous lesions. However, in one case in the present series in which necropsy was done, there was extensive infiltration of the lungs, pleura, epicardium, kidney, gallbladder and lymph nodes with myeloma cells but the skeleton was not involved.

Amyloidosis has been reported in about 10 per cent of the cases of multiple myeloma.[4,8,19] In the present study it was found in one of 13 cases in which autopsy was done. In that case there were amyloid deposits in the heart, blood vessels, skin, tongue and bone marrow. This distribution, rather characteristic of amyloidosis in multiple myeloma, is similar to that found in primary amyloidosis.

Renal histologic changes in multiple myeloma, first noted by Löhlein,[21] have been described many times. Some observers feel that they are almost pathonomonic.[5,20,23] The characteristic lesion is one of tubular obstruction by plugs of Bence-Jones protein. These casts may be wide, laminated and partially surrounded by giant cells or polymorphonuclear leukocytes. Hyaline droplets, granules or vacuoles may be noted in tubular cells. Bell[5] noted casts in 19 of 40 cases and felt that in 12 they were clearly the cause of renal insufficiency. In our study, casts were observed in renal tubules in six of thirteen cases in

which necropsy was done. Only in two, however, were large numbers of tubules so involved. In both the blood nonprotein nitrogen was normal. The kidneys of the patient with the highest nonprotein nitrogen content in the series (212 mg. per 100 cc.) had vacuolar changes in tubule cells, but tubular lumina contained only small amounts of amorphous eosinophilic material.

ANALYSIS OF SURVIVAL

Multiple myeloma is an invariably fatal disease. Nineteen patients in this study are dead (Table 4). The average duration of life in 18 patients after onset of symptoms was only nine months. Duration of the illness before diagnosis was established was 5.5 months; the average span from diagnosis to death, 3.5 months. Adding to this group one case in which the patient survived ten years increases the average survival time to 14 months. In three large series the average duration of life from onset to death was 19, 20 and 21 months.[4,27,19] The rather pronounced difference between the present series and these reported survival times is, perhaps, a reflection of the difference in types of hospitals from which the data were collected. Our material, drawn from a private hospital serving a local area, is perhaps more likely to contain a higher proportion of cases in which the patient survived a short time. The other series, all collected in medical centers, perhaps contained a higher proportion of long-surviving patients. Almost 60 per cent of the deaths in our series occurred in less than six months; and almost 90 per cent occurred within eighteen months. As previously mentioned, one patient survived at least ten years. Although this is decidedly uncommon, there are scattered reports in the literature of a few patients surviving from nine to sixteen years.[3,18]

DIFFERENTIAL DIAGNOSIS

Recognition of any rare disease requires that one know enough about it to distinguish it from the more common diseases that it superficially or closely resembles. In the present series of 26 cases, 11 different diagnoses were considered at the time of admittance of the patient to the hospital. Only in five cases was the diagnosis at admittance correct and in three of these it had been established by previous study elsewhere. Table 5, based in part on the ten incorrect diagnoses, presents the conditions commonly considered in the differential diagnosis of multiple myeloma.

Pathologic fracture, particularly in a middle-aged or elderly person, should lead to suspicion of multiple myeloma. Roentgenographically, senile or postmenopausal osteoporosis may closely resemble that seen in multiple myeloma. Compression vertebral

TABLE 4.—*Analysis of Survival (26 Patients)*

Dead	19
Living	4
Unknown	2
Moribund on admission; time of onset not known	1

Length of Survival (19 Patients)

Onset of Symptoms to Death	Number	Per Cent
0 to 5 months	11	58
6 to 11 months	2	11
12 to 17 months	4	21
18 to 36 months	1	5
10 years	1	5

Average Duration of Survival (18 Patients)

Before Diagnosis	Diagnosis to Death	Onset to Death
5.5 months	3.5 months	9 months

TABLE 5.—*Conditions with Similar Symptoms in Differential Diagnosis of Multiple Myeloma*

DISEASES
Pathologic fractures
Senile or postmenopausal osteoporosis
Metastatic carcinoma
Arthritis
Chronic nephritis
Spinal cord tumor
Hyperparathyroidism
LABORATORY ABNORMALITIES
Hyperglobulinemia
Rouleaux formation
Very high sedimentation rate
Unexplained anemia

fractures may occur in both. It is our impression, however, that the demineralization associated with multiple myeloma is likely to be more extreme and more painful than is this process when associated with senility or the postmenopausal state. Snapper[27] pointed out that the skeletal demineralization in postmenopausal osteoporosis is usually limited to the spine and pelvis, whereas in most cases of myeloma it is universal.

Osteolytic metastasis from carcinoma may very closely resemble the skeletal lesions in myeloma. The discovery of osteolytic metastasis should prompt immediate search for a primary lesion in those organs which frequently give rise to metastasis to bone, mainly kidney, thyroid, breast and prostate. It should be noted, however, that the lesions metastatic from carcinoma of the prostate are usually osteoblastic and pose no diagnostic difficulty. Also in the presence of osteolytic metastasis, the serum alkaline phosphatase content may be elevated; in multiple myeloma it is usually normal.

Because of the frequency of pain in the back in multiple myeloma, some patients are first believed to have spinal arthritis. As a matter of fact they may, for many are in an age group wherein degenerative changes of the spine are almost universal. In our experience the pain associated with degenerative arth-

ritis of the spine is usually of mild or moderate degree. Very intense or excruciating pain in a patient thought to have "arthritis" should make one skeptical of the diagnosis.

Because patients with multiple myeloma may have azotemia, albuminuria or anemia, they are frequently first believed to have chronic nephritis. However, as mentioned before, the "nephritis" associated with multiple myeloma is nonhypertensive. Bence-Jones proteinuria should be sought in all cases in which there is albuminuria or azotemia without hypertension.

Clinical features suggestive of a spinal cord tumor, notably weakness or paralysis of the lower extremities occurring in an adult, should make one wary of multiple myeloma. As mentioned before, multiple myeloma is second only to metastatic carcinoma among the noninflammatory lesions of the spine producing cord compression.

Hyperparathyroidism with skeletal involvement may closely resemble multiple myeloma. One patient in our series who was felt to have hyperparathyroidism had neck and mediastinal exploration for a parathyroid adenoma; none was found, but a marrow specimen removed by the surgeon from the sternum was histologically typical of multiple myeloma. It has been said that one can differentiate the two diseases by differences in the roentgen appearance alone.[27] However, since both of these conditions are quite rare, only in exceptional instances is a radiologist likely to have sufficient experience to be able to make this differentiation with confidence and accuracy. In both diseases, hypercalcemia may occur. However, in hyperparathyroidism—and not in multiple myeloma—there is also a decrease in serum phosphate and an increase in the serum alkaline phosphatase.

Finally, a very rapid blood sedimentation rate, rouleaux formation, or unexplained hyperglobulinemia or anemia should dictate bone marrow biopsy.

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